

What is claimed is:

1. A device for automatically selecting an aptazyme, the device comprising:

a programmable robot having at least one programmable robotic arm adapted for pipetting with disposable pipette tips; and

a worksurface accessible to the robot, the worksurface having modules comprising: at least one reservoir module for reagents, at least one pipette tip module, at least one magnetic bead separator module, at least one enzyme cooler module and at least one thermal cycler module;

wherein the programmable robot executes a program by which allosterically regulatable aptazymes are selected by exposing aptazyme libraries to an allosteric effector molecule.

2. The device of claim 1, wherein the robotic arm and the modules of the worksurface move in relation to each other, and the movement is unidirectional except to replenish the robot arm with a clean pipette tip.

3. The device of claim 1, wherein the worksurface is substantially stationary and the robotic arm programmably moves to each module to perform a programmed task.

5 4. The device of claim 1, wherein the robotic arm is substantially stationary and the worksurface programmably moves to align each module for access by the robotic arm to perform a programmed task.

10 5. The device of claim 2, wherein the robotic arm moves vertically.

15 6. The device of claim 3, wherein the robotic arm moves horizontally within the horizontal dimensions of a module aligned under the robotic arm.

7. The device of claim 1, wherein the device is programmed to:

20 incubate an aptazyme RNA pool in the presence of a biotinylated target conjugated to streptavidin magnetic beads and an allosteric effector molecule using a pipette tip-equipped robotic arm to combine the components of the incubation mixture;

expose the magnetic beads to the magnetic bead separator upon completion of incubation;
separate the beads from the incubation mixture; and
wash the beads to leave RNA bound to a target
5 attached to the beads.

8. The device of claim 1, wherein RNA oligonucleotides on the beads are:

reverse transcribed to produce DNA oligonucleotides;
10 the DNA oligonucleotides are amplified with the enzyme cooler and the thermal cycler; and
the DNA oligonucleotides are in vitro transcribed to produce RNA oligonucleotides.

15. The device of claim 1, wherein the device is adapted for selection of DNA oligonucleotides.

20. The device of claim 1, wherein the device is adapted for selection of modified RNA oligonucleotides.

11. The device of claim 1, wherein the device is adapted for selection of ribozymes.

12. The device of claim 1, wherein the device is adapted for selection of phage displayed proteins.

13. The device of claim 1, wherein the device is adapted for
5 selection of cell-surface displayed proteins.

14. The device of claim 1, wherein the device is used to detect biological warfare agents.

10 15. The device of claim 1, wherein the aptazyme comprises RNA.

16. The device of claim 1, wherein the aptazyme comprises DNA.

15 17. The device of claim 1, wherein the aptazyme is at least partially single stranded.

20 18. The device of claim 1, wherein the aptazyme is at least partially double stranded.

19. The device of claim 1, wherein the effector molecule is endogenous.

20. The device of claim 1, wherein the effector molecule is exogenous.

5 21. The device of claim 1, wherein the effector molecule comprises a protein.

22. The device of claim 1, wherein the effector molecule comprises a pharmaceutical agent.

10 23. The device of claim 1, wherein the effector molecule comprises a protein complex.

15 24. The device of claim 1, wherein expression of the target gene is up-regulated.

25. The device of claim 1, wherein expression of the target gene is down-regulated.

20 26. The device of claim 1, wherein the aptazyme is used to detect at least one exogenous effector molecule from a library of candidate exogenous effector molecules.

27. The device of claim 1, wherein the aptazyme and the effector molecule form an aptazyme-effector complex,

wherein the aptazyme-effector complex acts synergistically to effect the catalytic activity of the aptazyme-effector complex.

5 28. The device of claim 1, wherein the aptazyme and the effector molecule form a chimeric active site, and wherein the chimeric active site acts synergistically to effect the activity of the aptazyme.

10 29. The device of claim 1, wherein the aptazyme is used to determine the metabolic state of a cell.

15 30. The device of claim 1, wherein the aptazyme is used to detect at least one substance that perturbs cellular metabolism.

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31. An automated method for selecting aptamer oligonucleotides, the method comprising:

providing a programmable robot having a programmable robotic arm adapted for pipetting with disposable pipette tips;

providing a worksurface accessible to the robot, the worksurface having modules including reservoirs for reagents and pipette tips, a magnetic bead separator, an enzyme cooler and a thermal cycler;

10 preparing reagents including random pool RNA, buffers, enzymes, streptavidin magnetic beads and biotinylated targets;

providing disposable pipette tips;

15 preloading each reagent into a designated reservoir for each reagent;

preloading pipette tips into a designated reservoir of the worksurface;

programming the robot to perform a desired selection, including the steps of:

20 incubating an RNA pool in the presence of a biotinylated target conjugated to streptavidin magnetic beads and an allosteric effector molecule using a pipette tip-equipped robotic arm to combine the components of the incubation mixture;

exposing the magnetic beads to the magnetic bead separator upon completion of incubation;

separating the beads from the incubation mixture;

5 washing the beads to leave RNA bound to a target attached to the beads;

reverse transcribing the bound RNA to produce DNA oligonucleotides.

10 amplifying the DNA oligonucleotides with the enzyme cooler and the thermal cycler;

transcribing the DNA oligonucleotides in vitro to produce an RNA oligonucleotides;

executing the program; and

15 using the RNA oligonucleotide in iterative rounds of selection.

32. The method of claim 31, wherein the method is adapted for DNA selection.

20 33. The method of claim 31, wherein the method is adapted to modified RNA selection.

34. The method of claim 31, wherein the method is adapted to ribozyme selection.

35. The method of claim 31, wherein the method is adapted for selection of chimeras.

5 36. The method of claim 31, wherein the method is adapted for the diagnosis of disease.

37. The method of claim 31, wherein the method is adapted for the detection of biological warfare agents.

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38. A substrate that produces a signal when an aptazyme reaction occurs, the substrate comprising:

a solid support; and

15 at least one aptazyme construct comprising a regulatable aptamer oligonucleotide sequence having a regulatory domain, wherein the kinetic parameters of the aptazyme on a target gene vary in response to the interaction of an allosteric effector molecule with the regulatory domain;

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wherein the aptazyme construct is covalently immobilized on the support.

39. The substrate of claim 38, wherein the substrate is machine readable.

40. The substrate of claim 38, wherein the substrate comprises a multiwell plate.

5 41. The substrate of claim 40, further comprising beads in the wells.

42. The substrate of claim 41, wherein the aptazyme is covalently immobilized on the beads.

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43. The substrate of claim 38, wherein, upon occurrence of an aptazyme reaction in the presence of a detectable tag to be detected, the detectable tag is attached to the immobilized aptazyme to produce the signal.

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44. The substrate of claim 43, wherein the detectable tag comprises a fluorescent tag.

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45. The substrate of claim 43, wherein the substrate comprises an enzyme tag.

46. The substrate of claim 43, wherein the substrate comprises a magnetic particle tag.

47. A method for detecting an aptazyme reaction, the method comprising the steps of:

providing a substrate comprising a solid support and an aptazyme construct or a heterogenous mixture of aptazyme constructs covalently immobilized on the support;

providing at least one analyte;

providing a substrate tagged to be detectable;

exposing the substrate and at least one analyte to the immobilized aptazyme whereby the substrate is bound to the immobilized aptazyme upon activation of the aptazyme reaction by the analyte to produce a signal;

washing unbound substrate off of the substrate; and
detecting the signal from the bound substrate.

48. The method of claim 47, wherein the method is automated.

49. The method of claim 47, wherein the signal is amplified for detection.

50. The method of claim 47, wherein the aptazyme construct comprises modified nucleotides to inhibit degradation of the aptazyme.

51. The method of claim 47, wherein the aptazyme construct comprises modified nucleotides to inhibit degradation of the aptazyme.

5 52. The method of claim 47, wherein the aptazyme construct comprises modified nucleotides to inhibit degradation of the aptazyme.

10 53. The method of claim 47, wherein the aptazyme construct comprises modified nucleotides to inhibit degradation of the aptazyme.

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